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Probing for Cortical Excitability

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Abstract— **This paper introduces a new method for measuring cortical excitability using an electrical probing stimulus via intracranial electroencephalography (iEEG). Stimuli consisted of 100 single bi-phasic pulses, delivered every 10 minutes. Neural excitability is estimated by extracting a feature from the iEEG responses to the stimuli, which we dub the mean phase variance (PV). We show that the mean PV increases with the rate of inter-ictal discharges in one patient. In another patient, we show that the mean PV changes with sleep and an epileptic seizure. The results demonstrate a proof-of-principal for the method to be applied in a seizure anticipation framework.**

I. INTRODUCTION

This paper introduces a new method for measuring cortical excitability using intracranial electroencephalographic (iEEG) responses to an electrical probing stimuli. The aim of the paper is to relate the measurement of cortical excitability to electrographic epileptic events. There is substantial evidence that epileptic seizures are preceded by, or occur with, a temporary increase in cortical excitability (see below). Therefore, tracking cortical excitability may lead to a clinically viable seizure anticipation method.

The majority of previous approaches for seizure prediction/anticipation have used features from ongoing EEG recordings (passively observed) to track the 'state' of the brain. Although most methods are mathematically quite varied, the majority are conceptually similar and focus on measuring the degree of order within the brain. A decrease in order or complexity indicates abnormal hypersynchronous dynamics associated with a pre-seizure state. Earlier algorithms involved estimating entropy, correlation dimension, and short-term Lyapunov exponents [1], [2], [3], [4], [5]. The research focus shifted to synchronization analysis after the aforementioned methods failed to deliver repeatable results [6], [7], [8]. These algorithms have shown promise in certain patient groups, but they have not delivered reproducible outcomes and, therefore, have not provided satisfactory clinical performance [9], [10]. This motivates further research and a rethinking of the traditional seizure prediction framework, such as monitoring cortical excitability rather than measuring the degree of order within the brain.

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Epileptic hyper-excitability has been measured by a number of different modalities. It has been shown that there are major and prolonged changes in cortical excitability in the preictal time period using motor responses to transcranial magnetic stimulation (TMS) [11], [12], near infrared spectroscopy (NIRS) [13], functional magnetic resonance imaging (fMRI) [14], EEG auditory steady-state responses [15] and others. An important contribution in our understanding of preseizure excitability is from a study that used magnetoencephalographic visual steady-state responses to quantify preseizure excitability [16]. This research was later extended to incorporate electrical stimulation for patients with mesial temporal lobe epilepsy [17]. The results of the study demonstrated a clear relationship between iEEG responses to electrical stimulation and seizure occurrence. The increase in the neural response was attributed to hyper-excitability. Furthermore, it has been shown theoretically from a number of different stand-points that an active-EEG approach is required for tracking the preseizure neurodynamics [18], [19]. These studies support the new methodology presented in this current paper, which employs the active-iEEG paradigm for tracking cortical excitability in neocortical temporal lobe epilepsy.

II. METHOD

A. Patients

Data was collected from 2 patients undergoing evaluation for the surgical resection of epileptic foci at St. Vincent's Public and Private Hospital's in Melbourne, Australia. Data was collected under the appropriate ethics approval (HREC-A 006/08). The standard clinical practice for epilepsy related surgery involves a diagnostic period of one week, where intracranial EEG electrodes are implanted to map pathological oscillations in the electrical fields of the brain. In addition, the electrodes facilitate mapping of important functional brain tissue, such as speech and motor control, by observing behavioural responses to electrical stimulation.

B. Data Acquisition and Stimulation

In parallel to the standard clinical procedure, the research protocol was conducted to estimate cortical excitability. Electrical stimuli (delivered by a Grass S88x neurostimulator, Astro-Med) consisted of single bipolar, biphasic pulses delivered in groups of 100, with each pulse separated by 3.01s. A rest period of 5 minutes was included between each stimulation group. The pulse width was 100μs with current intensity of 2mA. The current intensity yielded a charge/phase of 0.2μC/phase and a charge density of

approximately 0.4μC/phase/cm^2 (for an electrode diameter of 4mm). This charge density is approximately 2 orders of magnitude below the well-documented safety limits of 30μC/phase/cm^2 [20], [21], [22], [23]. Stimuli were targeted to low-impedance electrodes, away from the cerebral vasculature, to the suspected epileptic foci and surrounding tissue.

All data was collected via intracranial grid electrodes (Ad-Tech medical). The data from the first patient (Patient 1) was collected from a 15×8 array of platinum disk electrodes with regular spacing in the x-direction of 5mm and 10mm in the y-direction. The data from the second patients (Patient 2) was from a 8×4 array with regular spacing of 10mm in both directions. Intracranial EEG was sampled at a rate of 5 kHz and the system (Synamp2, Compumedics) allowed for recording from a DC level (24-bit resolution), so transient responses to stimuli could be observed.

C. Signal Processing

When eliciting an observable response in the iEEG from a single pulse electrical stimulation, the recording resembles the early component of an evoked-response from an auditory (click) or visual (flash) evoked experiment. Naturally occurring evoked-responses are thought to be due to a phase reseting of the cortical oscillations [24]. Therefore, phase-locking measures are a logical choice for quantifying the level of response that is induced when using electrical stimulation.

The measure that we present in this paper is a novel measure, the mean phase variance (PV). The PV measures the inter-stimulus variation in the unwrapped instantaneous phase (IP). Essentially, the measure captures the variation in the instantaneous frequency of the responses. The motivation for using this measure is that we suspected that the PV would increase as hyper-excitable pathological tissue begins to drive and exert control over the normal oscillatory activity of the cortex. Other measures were explored in preliminary analyses, such as the phase-locking index, but the PV measure provided more stable results.

1) Pre-processing: Preprocessing and signal conditioning is required to ensure that noise has a minimal effect on the analysis. The first pre-processing step was to identify channels that had poor signal quality via visual inspection. Data from these channels were excluded from further analysis. Next, all epochs were visually inspected for artifact. Corrupted responses were excluded. Note, if inter-ictal discharges coincided with times when the stimulation was active, then that particular epoch was also excluded from further analysis. Next, 5 samples either side of stimulus time were removed from the time series, and reintroduced using linear interpolation. This removed the stimulus artifacts [25]. Next, the data was smoothed using a 10^{th}-order moving average filter. This step reduced sharp fluctuations and discontinuities in the signal that cause ringing when digital filtering is applied. The data was then 50 Hz notch filtered and low-pass filtered (cut-off $f_c = 95$ Hz) in the reverse time direction using a 2^{nd}-order Butterworth filter. Filtering in the reverse time direction ensured that any ringing induced by residual discontinuities from the stimulation appeared in the pre-stimulus time period. The data was then resampled from 5 kHz to 1 kHz and re-referenced to a differential montage, to remove common-mode interference and the effect of the reference electrode. Only neighbouring pairs in the x-y direction of the electrode, where both electrodes gave good signal quality, were used in the new montage. Following the preprocessing and filtering steps, the data was epoched about the time of stimulations.

Time intervals from 5 ms to 100 ms post-stimulation were used for analysis. Stimulation groups where greater than 50% of the epochs had obvious artifacts were excluded in order to gain reliable statistics from the interaction measures. This approach yielded at least 50 responses to stimulation, to form the excitability measures.

2) Instantaneous Phase Estimation: Estimation of the instantaneous phase is required to compute the PV measure. To estimate the IP, data must be filtered into narrow-band or semi narrow-band components [26]. Accordingly, semi narrow-band components of the iEEG were extracted via band-pass filtering. The centre frequencies for the results presented in this paper were 25 and 15 Hz for Patient 1 and 2, respectively, with a bandwidth of 10 Hz. Other frequency ranges were trialled in preliminary analyses, but these frequency ranges provided the best separation between epileptic and non-epileptic excitability estimates (based on visual inspection of results). The instantaneous phase, $\phi(n)$, was estimated by

$$\phi_{\alpha,\gamma}(n) = \arctan\left(\frac{\mathcal{H}y_{\alpha,\gamma}(n)}{y_{\alpha,\gamma}(n)}\right), \tag{1}$$

where $y(n)$ is the preprocessed, bandpass filtered EEG, α indexes the channels (in the differential montage), γ indexes the Γ (non-corrupted) stimulations in each 10 minute period, and n indexes the temporal sampling in the stimulation response period. The operator $\mathcal{H}$ denotes the Hilbert transform. Prior to computing the phase variance, the phase was shifted such that $\phi(0) = 0$ and the phase was unwrapped.

3) Phase Variance: Given the phase estimate, $\phi(n)$, the phase variance, $\sigma^2(n)$, for a given iEEG channel is

$$\sigma^2_\alpha(n) = \frac{1}{\Gamma}\sum_{\gamma=1}^{\Gamma}\left(\phi_{\alpha,\gamma}(n) - \bar{\phi}_\alpha(n)\right)^2, \tag{2}$$

where $\bar{\phi}_\alpha(n)$ is the mean of $\phi_{\alpha,\gamma}(n)$ over the Γ stimulations within the stimulation group. To reduce PV to a scalar quantity, the mean over the stimulus response period is taken. This gives the mean PV

$$\chi_\alpha = \frac{1}{N}\sum_{n=1}^{N}\sigma^2_\alpha(n), \tag{3}$$

where N is the number of samples in the response period.

III. RESULTS

In this section the results are presented, where we compare the PV excitability measure to epileptiform events. Note that all data was marked independently by an experienced neurophysiologist who was blinded to the signal analyses.

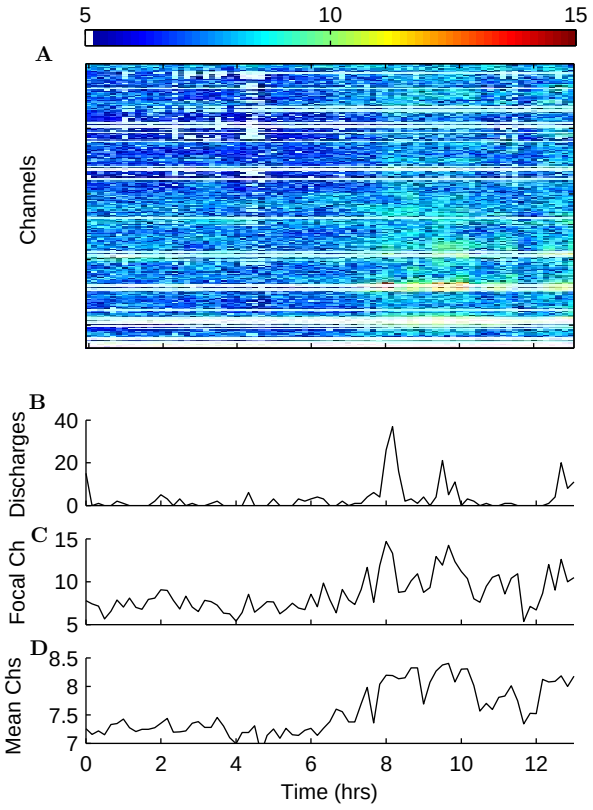

Fig. 1. The relationship of the excitability measure to the rate of inter-ictal discharges. A) The excitability measure for all channels over time. Warmer colours indicate higher PV value. The white space indicates where data was excluded due to noise or the channels were not recorded. B) The rate of epileptic discharges (per 10 min). C) The PV excitability estimate for a focal channel. D) The average excitability across all channels.

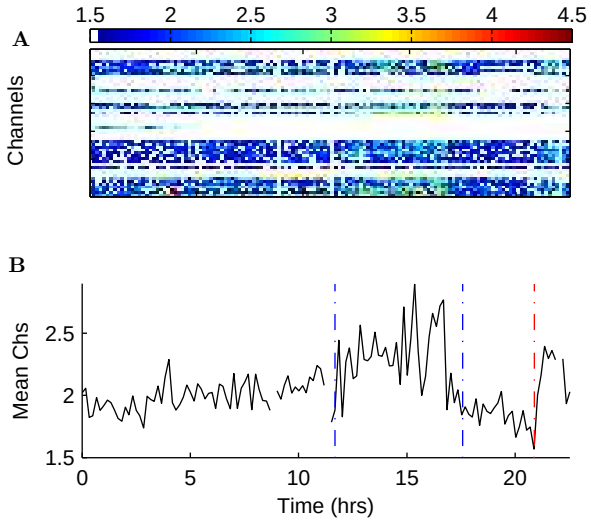

Fig. 2. The relationship between the excitability measure to sleep and a seizure. A) Excitability measurement for all channels over the experimental duration. Warmer colors indicate a higher PV value. The white spaces indicate where data was excluded due to noise or the channels were not recorded. B) The average excitability across all channels. The blue lines mark the boundary of a sleep period and the red line marks the onset of an epileptic seizure.

A. *Patient 1 - Excitability and Inter-Ictal Discharges*

For this patient we relate the PV measure for cortical excitability to the rate of inter-ictal epileptiform discharges. Stimuli were delivered to this patient for approximately 13hrs. During this time no clinical seizures occurred. Figure 1 shows the results from the analyses for all channel pairs. Figure 1 B shows the number of inter-ictal discharges (per 10 min block) over time. Figure 1 C shows the PV measure for a focal channel. Figure 1 D shows the average (across channels) PV measure, providing a global measure. The profile of the excitability measure follows a strikingly similar shape to the rate of discharges. This result provides evidence that the method was successful in tracking excitability for this patient. This holds under the assumption that the rate of discharges is proportional to the excitability level of the cortex.

B. *Patient 2 - Excitability and a Clinical Epileptic Seizure*

For this patient we relate the PV measure to sleep and an epileptic seizure. Figure 2 shows the results over a 23 hr period. The measure gave a stable output for the initial 12 hrs of stimulation when the patient was awake. During sleep, the phase variance increased. After waking and a few hours prior to a seizure occurring, the phase variance began to decrease. We suspect that the epileptic tissue had begun to take over the oscillatory activity in the cortex at this stage. The phase variance continued to decrease and was lowest at the time of the seizure. This result clearly demonstrates the potential for our method to measure excitability and anticipate seizures.

IV. DISCUSSION

This paper introduces a new method for tracking cortical excitability using an electrical probing stimulus. This work builds on other studies that use an active approach for measuring excitability, providing evidence that the use of an input stimulus may improve seizure anticipation algorithms. The current study is novel with respect to Kalitzin et al.[17]; they used steady-state responses from the mesial temporal lobe, where we use single pulse stimulation delivered to the neocortex. The study is novel with respect to Badawy et al. [11], as stimuli are targeted directly to the epileptic focus, and a more local measure of excitability is estimated.

A major benefit in using a single pulse input to track cortical excitability is the ability to average the responses to improve the signal-to-noise ratio (SNR). The improved SNR overcomes a major challenge in analyzing spontaneous EEG, where it is difficult to elucidate whether fluctuations in features are due to changes in excitability, spurious fluctuations from normal brain processes, or even noise.

A possible concern when using electrical stimulation for measuring excitability is safety. This issue was raised in response to the Kalitzin study [27]. In this regard, the authors would like to point out that the patients did not have any percept of the stimulus at any time during the experiments (including other preliminary studies not reported in this

paper). Further to this, the amount of charge delivered with the single pulse paradigm is less than scheduled therapeutic stimulators (see [28] for example).

Results from Patient 1 show an increase in the PV without the occurrence of seizures. This provides evidence that high excitability may not be a sufficient condition for seizures. However, high excitability may lead to a higher likelihood of seizures. This has implications for the standard seizure prediction framework, where false positives are penalized. The result for Patient 2 shows that the PV measure is consistently high during sleep, low prior to the seizure, and at the minimum during the seizure. Although we have a modest N of 1, this exciting result provides a proof-of-principal for our probing method of measuring excitability for seizure anticipation. The authors expect that the PV measure will vary across patients, as evidenced by the difference in the magnitudes across two patients in this study.

Future work should be focused on developing stimulation techniques to extract the maximum amount of information. For example, it is unclear whether stimuli should be targeted to the seizure focus or more remote cortical areas. Along similar lines, other features (besides the PV measure) should be explored to obtain more information about the excitability levels. Furthermore, the amount of information in the neural response may be maximized by incorporating a model-based analysis method, where estimated parameters will have a physiological meaning [29]. In the longer-term, we intend to extend this study and incorporate this technology into an ambulatory device. Now our focus is on further validation on a larger patient cohort.

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